

Microbial Champions: The Influence of Gut Microbiota on Athletic Performance via the Gut-Brain Axis

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Abstract: In recent years, exercise has shown a powerful ability to regulate the gut microbiota received with concern. For instance, compared with the sedentary group, high-level athletes showed a different gut microbiota composition and remarkable capability of physiological metabolism. In addition, different diet patterns (eg, high-fat diet, high carbohydrate diet *et.al*) have different effects on gut microbiota, which can also affect exercise performance. Furthermore, adaptations to exercise also might be influenced by the gut microbiota, due to its important role in the transformation and expenditure of energy obtained from the diet. Therefore, appropriate dietary supplementation is important during exercise. And exploring the mechanisms by which dietary supplements affect exercise performance by modulating gut microbiota is of considerable interest to athletes wishing to achieve health and athletic performance. In this narrative review, the relationship between gut microbiota, dietary supplements, training adaptations and performance is discussed as follows. (i) The effects of the three main nutritional supplements on gut microbiota and athlete fitness. (ii) Strategies for dietary supplements and how they exerted function through gut microbiota alteration based on the gut-brain axis. (iii) Why dietary supplement interventions on gut microbiota should be tailored to different types of exercise. Our work integrates these factors to elucidate how specific nutritional supplements can modulate gut microbiota composition and, consequently, influence training adaptations and performance outcomes, unlike previous literature that often focuses solely on the effects of exercise or diet independently. And provides a comprehensive framework for athletes seeking to optimize their health and performance through a microbiota-centric approach.

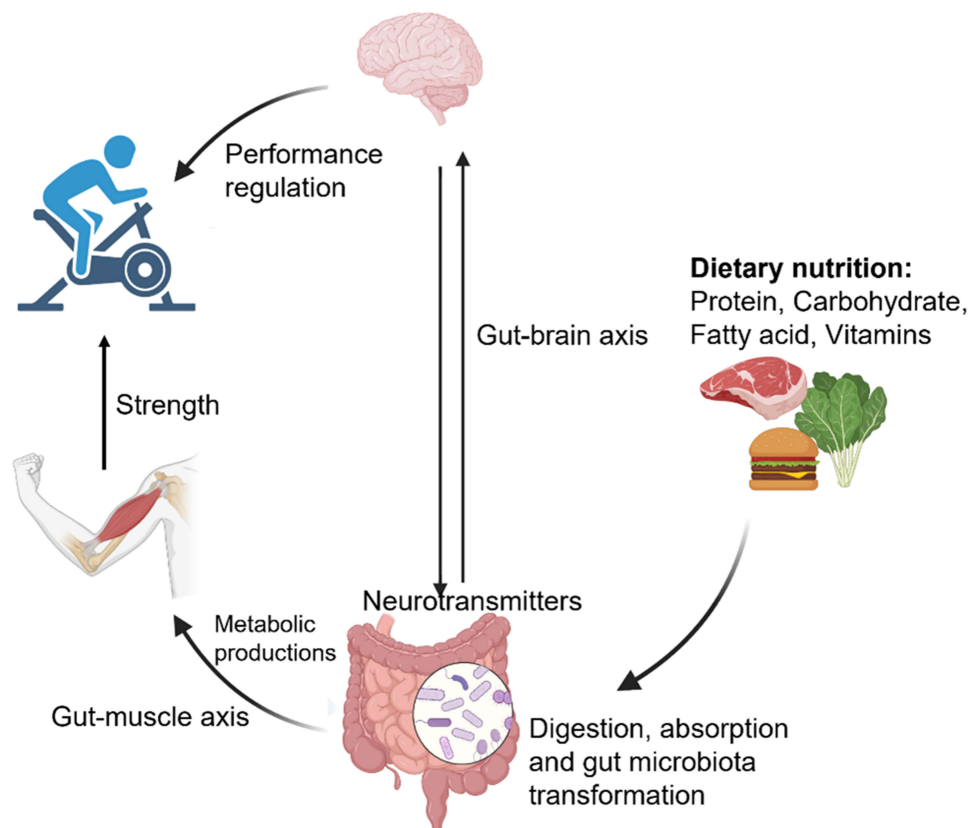
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Introduction

The gut is a niche inhabited by the human microbiota, with the largest number of bacteria and the greatest number of species. Consistent with the function of the digestive system, the gut microbiota (GM) harbors an enormous metabolic capacity and helps to absorb and transform the nutrients. The GM alteration has a strong association with human health status, for example, colorectal cancer patients showed a lower diversity of GM.¹ Lots of factors could shape the GM, such as birth mode, antibiotic use, and nutrient intake. Besides, a great diversity of metabolic ways can affect the GM, which results in highly dynamic and individualized shapes of the gut ecosystem, such as absorption of short-chain fatty acids (SCFAs), vitamin synthesis, energy harvesting, inflammatory regulation, and host immune response.^{2,3}

The nutrients are many and various, different nutrients that have a different effect on GM. For instance, researchers reported that rats fed a high-energy dense diet rapidly altered their GM with increases in *Firmicutes/Bacteroidetes* ratio and the abundance of pro-inflammatory *Proteobacteria* compared to those consuming a low-energy diet.⁴ Moreover, poor nutrition and a sedentary lifestyle are linked to a high incidence of chronic metabolic diseases,⁵ while exercise plays

Graphical Abstract



a fundamental role in preventing and treating these pathologies.⁶ Interestingly, studies also reported that the manipulation of GM and its by-products through exercise prescription might represent a promising novel approach in preventing and treating metabolic pathological conditions.^{7,8} Nowadays, one conception is that the GM acts like an endocrine organ, sensitive to changes in homeostasis and physiology associated with training. Exercise alone also causes large-scale changes in GM, which then increases cognitive capacity and provides some relief from symptoms in some disease models.⁹ In addition, a view that exercise promotes and helps maintain a healthy GM has gained momentum in recent years.¹⁰ Furthermore, reports demonstrated regular exercise is associated with higher biodiversity and the beneficial function of GM, and the GM may thus represent a mediator of the exercise-induced health benefits.¹¹

As a particular group, athletes significantly demand nutrition and exercise to pursue excellence. Hence, metabolic adaptations (including muscular strength and/or power, aerobic capacity, energy expenditure, and heat production) as well as the ability of the GM to absorb nutrients and regulate the immune system, are therefore particularly important at this juncture. In this process, GM exerted an important effect on athletic performance. For instance, researchers observed an increase in *Veillonella* relative abundance in marathon runners postmarathon, and the *Veillonella* methylmalonyl-CoA pathway is overrepresented. As a result, *Veillonella* species metabolize lactate into acetate and propionate via the methylmalonyl-CoA pathway, which acts to promote exercise performance.¹² Intriguingly, there is a high relevance between physical stress and changes in GM composition during exercise, specific microbiomes can correct various adverse events caused by strenuous exercise practice, which is associated with gastrointestinal discomfort, and training to exhaustion can also be associated with dysbiosis of the GM.^{11,13,14} Besides, acting as the mediator in the gut-brain axis, GM plays a critical role in this bi-directional and integrated system (Figure 1). It can help to secrete neurotransmitters and

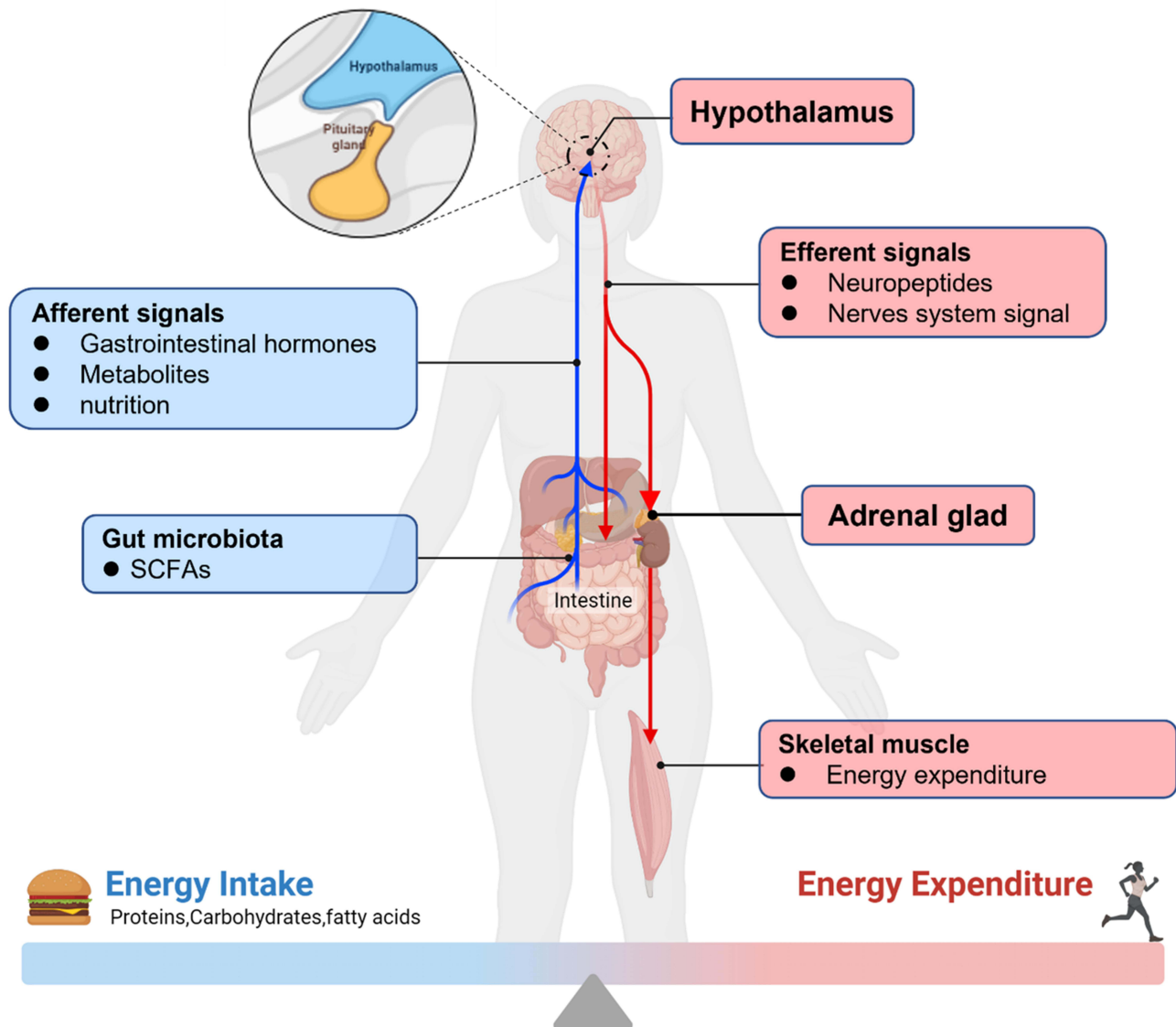


Figure 1 The mechanism of the gut-brain axis. Dietary nutrients are absorbed in the intestinal tract and interact with gut microbiota (GM) to synthesize neurotransmitters, which reach the central nervous system through the vagus afferent nerve. Neurons in the paraventricular nucleus of the hypothalamus secrete corticotropin-releasing hormone (CRH), which stimulates the anterior pituitary gland to release adrenocorticotropic hormone (ACTH). ACTH, in turn, prompts the adrenal cortex to synthesize glucocorticoids, which act on the skeletal muscle system via the vagus efferent nerve, participating in and enhancing the storage and utilization of skeletal muscle energy.

then through the hypothalamic-pituitary-adrenal (HPA) axis to maintain health and alleviate exercise depletion and oxidation.¹⁵

While moderate exercise generally benefits gut health, very intense or prolonged physical exertion can disrupt the delicate balance of the gut microbiota, potentially leading to dysbiosis¹⁶. This disruption may manifest as an increase in pro-inflammatory bacteria, a decrease in beneficial species, or both. For example, strenuous exercise has been linked to elevated levels of bacteria from the Enterobacteriaceae family, such as *Escherichia coli* and *Salmonella*. These bacteria are known to produce lipopolysaccharide, a potent endotoxin that can trigger systemic inflammation when it crosses a compromised gut barrier.¹⁷ Additionally, intense exercise may increase the abundance of *Desulfovibrio* species, which produce hydrogen sulfide, another pro-inflammatory compound.¹⁸ Several factors contribute to this phenomenon. During intense exercise, blood flow to the gut is reduced as it's redirected to working muscles. This can lead to intestinal hypoxia and increased intestinal permeability, potentially allowing harmful bacteria to cross the gut barrier and trigger inflammation.¹⁹ And the physiological stress of intense exercise can alter gut motility and hormone production, further

impacting microbial balance.¹⁴ This exercise-induced gut dysbiosis has been linked to gastrointestinal symptoms often experienced by athletes, such as cramping, bloating, and diarrhea, and may even impair recovery and performance in the long run. Thus, optimizing gut health through diet, supplements, and appropriate training load is crucial for athletes and active individuals to maintain muscle function, minimize inflammation, and support efficient recovery.

To compensate for athletes' increased energy consumption and maximize their adaptation to physical loads, they must adopt adequate dietary habits and nutritional supplements. Thus, we need to analyze the effects of mutual interactions between exercise, nutrient supplements, and GM on the overall general health and athletic performance to help them gain scientific guidance.

This narrative review offers new insights into the intricate interplay between gut microbiota, dietary supplementation, and athletic performance, emphasizing the role of the gut-brain axis. And moves beyond simply describing the impact of gut microbiota on muscle function. Instead, we delve into the crucial interplay between dietary supplements, training adaptations, and athletic performance, all mediated through the lens of the gut microbiome. By systematically exploring the impact of key dietary supplements on gut microbiota and outlining tailored strategies for their application based on exercise type, this review provides practical insights for athletes and practitioners seeking to optimize performance through targeted nutritional strategies.

The GM of Athlete Differs from Other Population

Since GM has a potential effect on performance-enhancing and in turn the exercise facilitates the GM alteration, in that way, the GM composition of athletes is certainly different from the other population (Table 1).

Several studies have explored differences in the composition of the GM between athletes and other populations (Table 1). A study of professional athletes from an international rugby union squad discovered that the athletes had lower inflammatory but improved plasma creatine kinase (an extreme exercise marker) and metabolic markers. Simultaneously, these professional athletes displayed a higher diversity of GM, which had a positive correlation with protein consumption and creatine kinase compared with control.²⁰

Table 1 The Effect of Different Types of Exercise on Gut Microbiota

Type of Exercise	Country, Sex, Age, and BMI	Method of Gut Microbiota Analysis	Effects
Professional rugby athletes ²⁰	All subjects except one (Indian ethnicity) were of Irish ethnicity. Male (n=40); Mean age: 29 (±4) years old; Mean BMI: 29.1 (±2.9). Healthy controls: Male; Mean age: 29 (±6) years old; Two groups with group 1 (n=23) having a BMI≤25 and group 2 (n=23) having a BMI >28.	By 16S rRNA amplicon sequencing.	Athletes have a higher diversity of gut microbes, representing 22 different phyla. <i>Bacteroidetes</i> were significantly less abundant in the athletes. Notably, the proportion of <i>Akkermansiacae</i> and <i>Akkermansia</i> in elite athletes was significantly higher than in the high BMI control group.
Professional rugby athletes ¹⁰	Professional male athletes (n=40) Healthy controls (sedentary subjects) (n=46): Two groups with low BMI (n=22, BMI≤25.2) and high BMI (n=24, BMI≥26.5).	Further statistical and bioinformatic analysis of the metagenome based on 16S rRNA replicate sequencing.	Enhancement of microbial diversity in athletes compared with controls. Athletes had relative increases short-chain fatty acids (SCFAs) and excreted proportionately higher levels of the metabolite TMAO.
Professional and amateur level competitive cyclists ²¹	All subjects were Americans. Professional group: Female (n=8); Male (n=14). Amateur group: Female (n=3); Male (n=8). Age: 19–49 (median age 33).	By metagenomic whole genome shotgun (mWGS) and metatranscriptomic (RNA-Seq) sequencing.	By mWGS sequencing, the 33 cyclists data of gut microbiomes split into three taxonomic clusters, marked by either high <i>Prevotella</i> , <i>Bacteroides</i> or a mix of many genera including <i>Bacteroides</i> , <i>Prevotella</i> , <i>Eubacterium</i> , <i>Ruminococcus</i> , and <i>Akkermansia</i> . Significant high abundance of the genus <i>Prevotella</i> (≥2.5%) was correlated with time reported exercising during an average week. Increased abundance of <i>Methanobrevibacter smithii</i> transcripts in a number of professional cyclists which comparison to amateur cyclists.

(Continued)

Table I (Continued).

Type of Exercise	Country, Sex, Age, and BMI	Method of Gut Microbiota Analysis	Effects
Bodybuilders ²²	All subjects were Korean and male. Bodybuilders (n = 15); Age: 25 (±3) years old; BMI=28.1 (±2.6). Elite distance runners (n = 15); Age: 20 (±1) years old; BMI=20.5 (±0.8). Healthy control (without exercise habits) (n = 15); Age: 26 (±2) years old; BMI=25.9 (±4.2)	The DNA of fecal samples was sequenced for the analysis of gut microbial diversity through bioinformatics cloud platform.	Highest level of <i>Faecalibacterium</i> , <i>Sutterella</i> , <i>Clostridium</i> , <i>Haemophilus</i> , and <i>Eisenbergiella</i> in bodybuilders, while <i>Bifidobacterium</i> and <i>Parasutterella</i> were the lowest. For species, intestinal beneficial bacteria widely used as probiotics (<i>Bifidobacterium adolescentis</i> group, <i>Bifidobacterium longum</i> group, <i>Lactobacillus sakei</i> group) and those producing short chain fatty acids (<i>Blautia wexlerae</i> , <i>Eubacterium hallii</i>) were the lowest in bodybuilders and the highest in controls.
Elite Race Walkers ²³	All subjects from Australia, Canada, Chile, Italy, Japan, Poland, South Africa, and Sweden. Male (n=30) Age: 20–35 years old	By 16S rRNA amplicon sequencing.	The microbiota profiles at the beginning could be separated into either a <i>Prevotella</i> or <i>Bacteroides</i> dominated enterotype. The Low Carbohydrate High-Fat diet resulted in a greater relative abundance of <i>Bacteroides</i> and <i>Dorea</i> and a reduction of <i>Faecalibacterium</i> .
Marathon runners ²⁴	Female and male (n=15); Sedentary controls (n=10)	By 16S rRNA amplicon sequencing.	After a marathon an increase in <i>Veillonella</i> and every gene in a major pathway metabolizing lactate to propionate is at the higher relative abundance in marathon runners.
Professional Wushu routine martial arts athletes ²⁵	All subjects were Chinese. Female (n=15), Male (n=16), Age: 20–24 years old. Two groups with 12 higher-level and 16 lower-level athletes	By 16S rRNA amplicon sequencing.	Higher-level athletes' gut microbial richness diversity was significantly higher than in the lower-level athletes. The genera <i>Parabacteroides</i> , <i>Phascolarctobacterium</i> , <i>Oscillibacter</i> and <i>Bilophila</i> were enriched in the higher-level athletes. The genus <i>Megasphaera</i> , on the other hand, is abundant in low-level athletes.
Strength athletes ²⁶	Polish, Male (n=16), Aged from 19 to 24 years or older.	High-throughput sequencing	<i>Alistipes communis</i> species showed an increase in abundance during the Wingate test (WT) specifically within the strength group, indicating a potential link to resistance training. <i>Dorea longicatena</i> , <i>Catenibacterium</i> sp AF22 15, and <i>Clostridium phoceensis</i> were identified as more abundant in strength athletes at various time points of analysis
Endurance athletes ²⁶	Polish, Male (n=15), Aged from 19 to 24 years or older.	High-throughput sequencing	<i>Blautia</i> sp AF19 10LB, which was found to be significantly more abundant in endurance athletes compared to both the strength and control groups at most time points. The presence of <i>Bacteroides faecis</i> , <i>Fusicatenuibacter saccharivorans</i> , and <i>Ruminococcus</i> sp AF419 was also noted at different intervals, indicating their potential role in endurance performance

Another novel study showed a trend towards a decrease in GM diversity following a systematic reduction in training in swimmers, suggesting that GM is susceptible to change following changes in exercise levels.²⁷ In addition, *Coprococcus* and *Faecalibacterium* were also reduced during this process. *Faecalibacterium* was found to be enriched in athletes,²⁰ where it helped to reduce oxygen tension in the lumen and produce butyrate.²⁸ In previous reports, these microbiomes have been associated with increased physical activity and improved gut health through the fermentation of complex carbohydrates, which are also responsible for providing energy to the host.²⁹ In addition to the normal population, in a cross-sectional study of females, researchers observed the highest alpha diversity in athletes compared to anorexia nervosa patients, overweight, obese and normal weight controls, and the lowest diversity in anorexia nervosa patients,³⁰ possibly due to inadequate nutritional intake and physical activity.

Not only the GM of the athlete is different from the normal population but also there is a difference between the athletes. The professional athletes had distinct taxa composition characteristics and subsequently had functional metabolism features in the gut microbiota. Among professional martial arts athletes, a total of 10 different taxa of microorganisms were commonly found in high- and low-level athletes.²⁵ Typical examples in high-level athletes are *Parabacteroides* and *Phascolarctobacterium*, while the *Megasphaera* (belonging to family *Veillonellaceae*) has been most extensively studied in low-level athletes. Whereas *Parabacteroides* could bring advantages to exercise and cardiac

function, furthermore, they were negatively associated with metabolic disorders.^{31,32} However, *Megasphaera* has a relevance to nonalcoholic steatohepatitis and genital tract inflammation,³³ and also a potential to produce high levels of lipopolysaccharides.³⁴ That may suggest the elite athletes had more beneficial and abundant microbial taxa characteristics compared to low-level athletes, and these characteristics are associated with levels of physical activity to a certain extent.³⁵ In a survey of cyclists, the majority of cyclists (30 out of 33) had *Akkermansia*, and the relative abundance of *Prevotella* among them was high in cyclists who trained for more than 11 hours per week.²¹ Among professional cyclists, *Methanobrevibacter smithii* had a higher probability of occurrence than at the amateur level. An important role of *M. smithii* is the fermentation of complex polysaccharides, through its utilization of hydrogen gas (H₂) and formate to reduce carbon dioxide (CO₂) to methane.^{36,37} Once *M. smithii* disappeared, accumulated H₂ will inhibit bacterial NADH dehydrogenases and then decrease the production of ATP, SCFAs, and other important compounds.^{36,37} Another stratification of athlete GM analysis showed that different levels of athletes have a different GM enterotype, in the aspects of taxonomical structure and functional composition, the majority of elite athletes assigned to a similar enterotype.³⁸ An enterotype-dependent GM is strongly associated with athlete performances. Further in-depth functional profiling revealed that elite athletes have an excellent in ATP metabolisms, multiple sugar transport systems and carbohydrate metabolisms depending on their enrichment microbial community.³⁸ Raised evidence revealed elite athletes are more tolerated various kinds of stress and overload,³⁹ the reason is elite athletes have a better GM community that can modulate excitatory and inhibitory neurotransmitters and neurotransmitters-like substances, especially in response to physical and emotional stress.^{40,41}

GM Helps to Strength Skeletal Muscles to Enhance Exercise Performance

It is self-evident how important skeletal muscles are to exercise or athletes' performance. The requirement for skeletal muscle mass and function is widespread in all types of exercises/sports. Strength exercise depends on the explosive strength of the muscles and endurance exercise requires aerobic capacity and muscle metabolic ability to improve endurance. Dietary intake is undoubtedly the main factor influencing the deposition of muscle proteins. But recent research suggests a role for the GM in regulating skeletal muscle mass and function in mice. Furthermore, the gut microbiome may also influence muscle function through the regulation of the immune system and related gene expression.⁴² Compared to pathogen-free mouse skeletal muscle, germ-free (GF) mouse skeletal muscle showed atrophy, decreased expression of insulin-like growth factor 1 (IGF-1), reduced transcription of genes associated with skeletal muscle growth and mitochondrial function, and reduced expression of genes encoding *Rapsyn* and *Lrp4*, which are important proteins for neuromuscular junction assembly and function.⁴² Transplanting the GM from pathogen-free mice into GF mice could convert this situation.⁴² One of the potential mechanisms is GM could modulate the muscle mass and function through the gut-muscle axis. For example, *Lactobacillus curvatus* CP2998 exerted a positive effect on muscles by suppressing glucocorticoid receptor activation and the improvement of glucose utilization.⁴³ In contrast, the evidence showed the gut microbiome may influence skeletal muscle via catabolic pathways. For instance, metabolites produced by the gut microbiota, such as trimethylamine N-oxide, have been linked to increased inflammation and oxidative stress, which can negatively impact muscle function and recovery.^{19,44–46} Besides, a healthy GM (eg, *Propionibacteria* and *Lactobacillus reuteri*) can produce significant amounts of folate and vitamin B12, which may improve muscle anabolism and prevent hyperhomocysteinemia-induced oxidative stress and endothelial damage.⁴⁷ Another work focused on periodic diet strategies commonly used by athletes, which are, low-carbohydrate high-protein diet during physical training to improve fitness, and high-carbohydrate diets during competitions to improve athletic performance. The result showed GM stability was associated with greater athletic performance when highly trained individuals underwent dietary periodization.⁴⁸ These changes in the GM may also help to reduce inflammation and improve muscle function and recovery processes.

Different Nutrients Intake Interacts with GM and Influence Exercise Performance

Both professional and amateur athletes take dietary supplements to help improve their performance. Athletes have always preferred different dietary patterns due to the different types of sports they play. According to a study of bodybuilders and distance runners, researchers found the bodybuilders prefer a high protein, high-fat and low carbohydrate/dietary fiber diet, while distance runners prefer a low carbohydrate and low dietary fiber diet.²² *Faecalibacterium*, *Sutterella*, *Clostridium*, *Haemophilus*, and *Eisenbergiella* were found to be more abundant in bodybuilders, while abundance of *Bifidobacterium* and *Parasutterella* were less abundant. Meanwhile, some probiotics used as dietary supplements, such as *Bifidobacterium adolescentis*, *Bifidobacterium longum*, and *Lactobacillus sakei*, were at the lowest levels in bodybuilders.²² This may be related to a dietary pattern of plentiful protein intake. Cross-sectional studies confirmed that only long-term diets were associated with enterotype clustering compared to short-term.⁴⁹ Based on the type of nutrients, further discussion will be categorized as follows (Figure 2) (Table 2).

Protein

When talking about athletes or sports, protein supplementation is always on our minds. Indeed, protein supplementation helps to increase muscle mass and strength gains during exercise.⁶¹ However, malondialdehyde (MDA) levels are a marker of oxidative stress and are associated with excessive protein intake in resistance-trained athletes, with higher

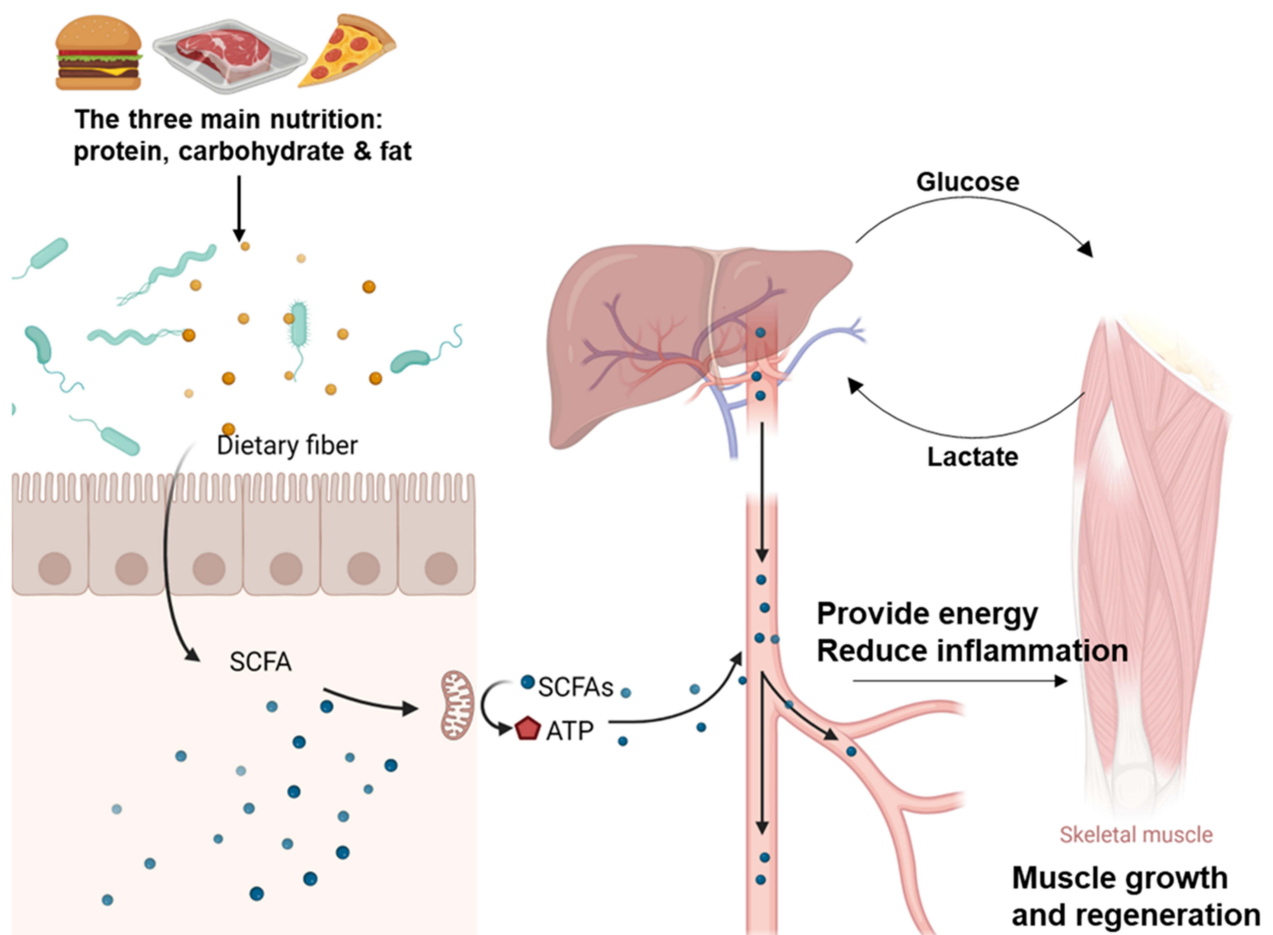


Figure 2 The three main nutrition effect on GM to provide the energy. The three main nutrition altered the gut microbiota (GM) composition to exert anti-inflammatory properties and provide the energy. Short Chain Fatty Acids (SCFAs) play an important role in glucose and lactate metabolism, it has been shown to increase the 5' adenosine monophosphate-activated protein kinase (AMPK) activity in liver and muscle tissue then triggers peroxisome proliferator-activated receptor (PPAR) gamma coactivator-1 α expression, to control the transcriptional activity of several transcription factors and subsequently to regulate cholesterol, lipid, and glucose metabolism.

Table 2 The Effect of Different Nutrients and/or Diets on the Gut Microbiota

Nutrient and/or Diet	Daily Intakes	Type of Gut Microbiota	Effects
Protein (g)	≥200 (Median 248) ²⁰	<i>Akkermansiaceae</i> and <i>Akkermansia</i> are predominant. <i>Prevotellaceae</i> , <i>Erysipelotrichaceae</i> , S24-7, <i>Succinivibrionaceae</i> , <i>Prevotella</i> , and <i>Succinivibrio</i> groups showed the biggest flux changes in relative abundance.	Exercise and protein intake drive gut microbiota diversity among athletes.
Carbohydrate (g/kg/d)	8.5 ⁵⁰		A high-carbohydrate diet does not improve immune function or prevent a decrease in plasma glutamine concentrations following extensive training. ^{51,52} Simple and refined carbohydrates are not conducive to healthy gut microbiota composition or the production of beneficial SCFAs. ⁵³
Fat	20%-35% total energy ⁵⁴ An athlete's fat consumption tends to be quite high (15–30% of dietary energy). ⁵⁵ During prolonged exercise, endurance may benefit from a fat intake of 30–50% of dietary energy. ⁵⁶	High-fat and high-calorie diets increases intestinal permeability and plasma LPS along with a decrease in total bacterial density and an increase in the relative proportion of <i>Bacteroidales</i> and <i>Clostridiales</i> orders. ⁵⁷	Diets high in fat may also alter the gut microbiota unfavorably.
Polyunsaturated fat	Taking approximately 1–2 g of omega-3 polyunsaturated fatty acids daily, with eicosatetraenoic acid and docosahexaenoic acid proportions of 2:1, is optimal. ⁵⁸		During exercise, eicosanoids, cytokines, and ROS are decreased.
Fiber	Athletes trained in endurance consume less than 25 g a day. ⁵⁹	Microbiota diversity, SCFA production, and anti-pathogenic bacteria are reduced when fiber consumption is low. ⁵⁶	During the recovery period and training period, athletes should decrease the energy from processed foods high in added sugars, refined carbohydrates, and fat, since eating a high-fiber diet before intense training or competition could produce GI upset such as distension, gas, and bloating. ¹⁴¹

levels of protein intake leading to lower malondialdehyde levels.⁶² Some researchers believe that long-term protein supplementation may impair GM. Overfeeding protein caused butyrate concentrations to decrease in fecal samples, suggesting a possible negative effect of a high-protein intake on colon health.⁶³ Furthermore, the butyrate can significantly reduce the levels of MDA thus protecting the host from oxidative damage.⁶⁴ That may indicate overfeeding protein will reduce the butyrate concentration and result in a high-level MDA in our body.

Proteolysis produces α -amino acids, most α -amino acids are unable to synthesize by humans or synthesize at a rate far from the body's needs, which must be supplied by the extra food proteins. Among the α -amino acids, branched-chain amino acids and taurine are the most common functional sports drinks, which help athletes enhance the anabolic and adaptive effects of exercise on skeletal muscle and improve recovery ability.^{65,66} However, it does not imply that the more taurine consumed, the more energy gained. In case of proteolytic metabolite production beyond the hosts' ability to assimilate, transform, or detoxify harmful metabolites, adverse effects on intestinal barrier function, inflammation, and

colonic health will occur.⁶⁷ Evidence suggests that overfeeding of taurine has an association with colorectal cancer and is due to its ability to elevate taurocholic acid, deoxycholic acid, and hydrogen sulfide concentrations.⁶⁸

GM also plays an important function in protein absorption and energy metabolism through the gut-muscle axis. For example, *Lactobacillus paracasei*, is a probiotic that can enhance the bioavailability of plant proteins by elevating essential amino acid concentrations.⁶⁹ Another probiotic, *Bacillus coagulans* (GBI-30,6086), shows anti-inflammatory properties and produces proteases to aid the absorption of amino acids by the host.⁷⁰ However, there are two different results in detecting the protein intake and alteration of GM in athletes. Clarke et al²⁰ draw a conclusion that overfeeding of protein supplementary enhanced the GM diversity, but Jang et al²² demonstrated it decreased the GM diversity. However, this may be attributed to the different fiber intake between athletes, and the fibre intake exerts a great impact on GM too.

As mentioned above, protein intake is a necessary supplement for athletes, but overfeeding of protein may have the opposite effect. Appropriate supplementation of probiotics to enhance protein metabolism may be a safe and reliable solution to maximize protein utilization and enhance athletic performance.

Carbohydrate

As the main source of energy for long-distance running races, endogenous carbohydrates are stored in the liver and muscle, and glycogen requires catabolic reactions for proper energy production in the liver and muscle cells.^{71,72} It has been recognized that the intake of a high carbohydrate (CHO) diet can improve endurance performance. Therefore, it is recommended that endurance athletes maximize CHO availability to enhance their performance during endurance sports competitions.⁷³ However, in the past several decades, the conception of the CHO has changed in the competition sports field. New guidelines in recent years have stated that a universal recommendation of absolute CHO intake is inappropriate.^{74–76} The key points are threefold. Firstly, competitive exercise is highly variable, so CHO should be prescribed according to the expected fuel requirements of the exercise or sport. Secondly, high CHO intake is necessary and beneficial during high intensity or endurance exercise, but when exercise intensity becomes lower, consistent high CHO supplementation seems less important. Finally, how and when to supplement with CHO should consider the cyclical requirements of training and competition and be individualized.

To improve the performance of competitive sports, a new alternative view—a low-carbohydrate, high-fat (LCHF) diet has been come up to increase the fat utilization of muscle and the aerobic capacity of athletes. But that may impair performance in elite endurance athletes. A meta-analysis revealed a weak effect of ketogenic LCHF diet interventions through the index of maximum oxygen uptake (VO₂max), rating of perceived exertion (RPE), time to exhaustion (TTE), maximal heart rate during exercise (HR_{max}), and rating of perceived exertion (RPE), but a significant effect on the respiratory exchange rate (RER).⁷⁷ Burke et al illustrated that the LCHF impairs performance in elite endurance athletes although a significant improvement in peak aerobic capacity.⁷⁸ Although a short-term adaptation to an LCHF diet in elite athletes increased exercise fat oxidation, it was not further enhanced with longer periods of exposure; nevertheless, the economy of exercise at intensities relevant to real-life endurance events is reduced by brief adaptation to a ketogenic LCHF when fat oxidation is maximized.⁷⁹ This suggests that the LCHF major increased the capacity for fat oxidation in the host physiology, it is not conducive to endurance exercise at sustained high intensity, where oxygen delivery to the muscles becomes limited.

For now, it's too early to say whether taking carbohydrates is beneficial or negates the performance of athletes. As the main resident of the gut, GM exerted a critical role in carbohydrate metabolism. Nida Murtaza et al divided elite race walkers into three groups: High Carbohydrate (HCHO), Periodised Carbohydrate (PCHO), and ketogenic Low Carbohydrate High Fat (LCHF) diet. After three weeks of intervention, LCHF decreased the abundance of *Faecalibacterium* and increased the relative abundance of *Bacteroides* and *Dorea* and showed significant negative correlations were observed between *Bacteroides* and fat oxidation.²³ While the production of *Faecalibacterium prausnitzii* includes a suite of metabolites and peptides with anti-inflammatory effects.⁸⁰

Short-chain fatty acids (SCFAs) are the end product of fermentation of undigested carbohydrates and fiber from the diet by anaerobic gut microbiota. Significantly, SCFAs have gained sufficient attention in terms of GM alteration, health

maintenance and athlete performance. There is growing evidence that SCFAs exert a variety of beneficial effects on energy metabolism, anti-tumor, anti-inflammatory, immune homeostasis and anti-pathogens in mammals.^{81–84}

Athletes in the rankings, especially endurance athletes, rely on effective and efficient energy metabolism to enhance their performance. The report found that GF mice were significantly less capable of endurance exercise compared to mice with SCFAs-producing bacteria — *Bacteroides fragilis* in their colon.⁸⁵ This raises the hypothesis that the contribution of GM to aerobic activity may come from SCFAs. In animal experiments, hypoxia-induced remodeling of the intestinal microenvironment, which enhances SCFAs concentrations by increasing the abundance of related genera such as *Akkermansia* and *Bacteroidetes*.⁸⁶ The supplementation of acetate and butyrate significantly increased the biogenesis of muscle mitochondria. This may suggest that endurance capacity is enhanced by high concentrations of SCFAs in hypoxic conditions.⁸⁶ Another experiment also confirmed that multiple antibiotics treated in mice increased their exercise capability after continuous acetate infusion.⁸⁷ The depth analysis expounded that SCFAs may actively interfere with the mitochondrial biogenesis in the skeletal muscle. In addition, SCFAs have been shown to increase the adenosine 5'-monophosphate-activated protein kinase (AMPK) activity in liver and muscle tissue, which then triggers peroxisome proliferator-activated receptor gamma coactivator (PGC)-1 α expression, and subsequently control the transcriptional activity of several transcription factors such as peroxisome proliferator-activated receptor (PPAR) α , PPAR γ , PPAR δ , liver X receptor (LXR), and farnesoid X receptor (FXR), which are all important in the regulation of cholesterol, lipid, and glucose metabolism.^{82,88}

Fat

As we all know that both carbohydrates and fat are important substrates for oxidative phosphorylation and energy production in skeletal muscle. In exercise or competitive sport, lipid utilization is not the physical availability of fat to provide the energy but to bring the lipid to the site of oxidation in the muscles to furnish energy by the oxidative processes.⁸⁹ During the exercise, the main fuel substrates for athletes are triglycerides and adipose tissue.⁹⁰ Fat ingested from food is absorbed by intestinal mucosa under the action of bile acid lipase, and exogenous triglycerides are synthesized in intestinal mucosal epithelial cells. Triglycerides are stored in skeletal muscle cells as fat droplets. The content of triglyceride in skeletal muscle is affected by muscle fiber type, nutritional status, physical activity, and other factors. In addition, Intramuscular triglycerides are also thought to be an important source of substrate formation during prolonged endurance exercise in trained men. A study of trained men found that after prolonged endurance cycling, the intramuscular triglyceride content in the muscle was significantly reduced.⁹¹

In a study of high-fat diet and exercise training, untrained volunteers consumed a high-fat diet or high carbohydrate diet for 7 weeks and meanwhile with an aerobic endurance training program. The results indicated the activity of β -hydroxyacyl-coenzyme A dehydrogenase was increased by 25% which may suggest that diet can affect muscle enzymatic adaptation, presumably through an effect on the substrate flux and enhanced fatty acid (FA) metabolism, permitting enhanced FA oxidation.⁹² But the intake of fat should also consider the type of fat, body composition, sport modality, training level, intestinal microenvironment, and so on. The amount and different types of fat are crucial for athletes' performance and the health of GM.^{90,93}

For instance, the omega-3 fatty acid appears a potential function of influencing the metabolic response of muscle to nutrients and physiological functional response to exercise and post-exercise conditions, helping recovery and decreased injury/reduced risk of illness in athletes.⁹⁴ Further study also explored whether the omega-3 fatty acid influenced the GM. The GM occurred alteration after an omega-3 fatty acid supplement in humans. It decreased the abundance of *Faecalibacterium*, which have relevance to an increase in the Bacteroidetes and butyrate-producing bacteria.⁹⁵ This is consistent with the results we mentioned above that LCHF diet interventions altered the GM composition, both decreasing the *Faecalibacterium* and increasing the *Bacteroidetes*. In addition, the mountain of evidence illustrates that omega-3 has a positive action on the host, such as anti-inflammatory, helps to maintain the gut barrier, regulates the immune system, and interestingly, it could also increase the production of SCFAs.^{96,97}

Vitamin

Most vitamins cannot be synthesized or not produced in sufficient quantities to satisfy the body's needs and must be obtained frequently from food, once the lack will cause vitamin deficiency disease and damage to human health (Figure 3). GM exerts a critical role in the process of vitamin synthesis. In athletes, vitamin deficiency causes long-term adverse cardiovascular effects, muscle damage, inducing high oxidative stress et al^{98,99} Vitamins are a large family, and now we will discuss only a few representative ones.

For instance, vitamin D affects calcium and phosphate transport by muscles through cell membranes, phospholipid metabolism, and muscle cell proliferation and differentiation.¹⁰⁰ It is essential for skeletal calcium deposition and maintaining the balance of blood calcium. In the process of vitamin D synthesis, GM influences the vitamin D metabolism embodied in inhibiting fibroblast growth factor 23 and induced increased serum 25-hydroxyvitamin D, 24,25-dihydroxyvitamin D, and 1,25-dihydroxyvitamin D levels.¹⁰¹

In the vitamin B family, B2, B9 (Folate), and B12 are most strongly associated with exercise. B2 can improve redox reactions and energy production. Folate and B12 can prevent homocysteine-induced oxidative stress and endothelial damage.¹⁰² The main strains of GM to help synthesize them include *Bacillus subtilis*, *Escherichia coli*, *Bifidobacteria* (main synthesis B2), *Bifidobacteria*, *Lactobacilli* (main synthesis folate), and *Propionibacteria*, *Lactobacillus reuteri* (main synthesis B12).⁴⁷

The alterations in the oxidant/antioxidant balance are key factors in excessive reactive oxygen species (ROS) accumulation, and ROS accumulation can cause skeletal muscle injury.¹⁰³ Supplementing vitamins properly (eg, vitamin E) can interrupt lipid peroxidation reactions and remove free oxygen radicals, stabilizing cell membranes to alleviate muscle injury.¹⁰⁴ Studies in animals and humans show that GM can synthesize vitamin C and K and the B group vitamins.¹⁰⁵ Although it is not synthesized by GM, vitamin E has been demonstrated to alter the GM composition and protect the gut barrier integrity by inhibiting the loss of tight junction proteins.¹⁰⁶ Hence, further investigation is required for effective interventions targeting the GM composition and vitamin levels, to determine the mechanisms underlying vitamin regulation by the GM.

Summary

The four main nutrients do not play a single role in GM and exercise, and many athletes have their special eating habits. In terms of dietary choices, it is also impossible to achieve a single intake, for example, fat intake is usually accompanied

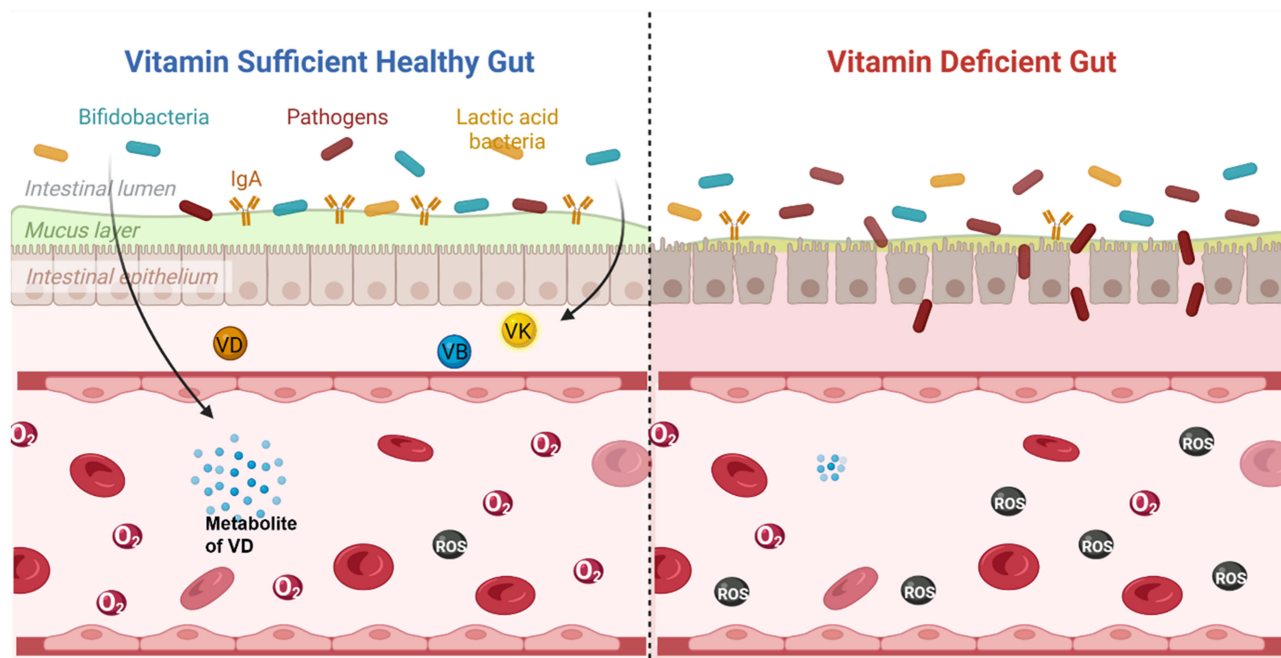


Figure 3 The effects of vitamin on athletes. The beneficial gut microbiota (GM) species can help to synthesize the vitamins to decrease the Reactive Oxygen Species (ROS) accumulation, interrupt lipid peroxidation reactions and remove free oxygen radicals, stabilizing cell membranes to alleviate the muscle injury.

by carbohydrate and ketogenic pattern. Athletes have a large requirement for energy intake, and different sports require different energy and nutrients, such as endurance sports and burst strength sports, they have a different diet pattern. This requires full consideration of athletes' physique and sports need in the process of nutrition intake and collocation. In such cases, it is important to fully consider the role of GM in digestion, absorption, metabolism, and athletes' performance.

Nutrient delivery to the gut activates neuroendocrine mechanisms that control digestion and energy intake and utilization with the help of GM. GM can secrete vary such enzymes to help digestion and absorption and ferment fibers that cannot be absorbed by intestinal epithelial cells. These fibers ferment to produce SCFAs that are vital to the body, on the one hand, SCFAs are indispensable in maintaining colon health and act as an energy source for colonocytes. On the other hand, it is a neurotransmitter in gut-brain axis. In addition, GM also releases other mediators, including 5-hydroxytryptamine (5HT), glucagon-like peptide-1 (GLP-1), Peptide YY act on vagal afferent neurons regulating food intake and digestion.¹⁰⁷ A novel study reveals a new mechanism of GM that regulates digestion and absorption. They found that bacterial sensing via neuronal Nucleotide-binding oligomerization domain 2 (Nod-2) regulates appetite directly.¹⁰⁸ In other words, the bacteria in the gut can also manipulate people, making them crave what they want. To sum up, the GM has three main ways to influence the digestion: (i) To produce the enzymes to help digestion. (ii) To produce the neurotransmitters and regulate digestion through the gut-brain axis. (iii) Sensing of bacterial cell wall components by brain neurons directly to regulate the digestion. In short, GM may be more important in some ways than the brain in regulating and controlling appetite.

The Strategy of Diet Supplements

In the view of the above, it seems feasible to focus dietary supplementation on altering the gut microbiota. Numerous clinical and animal studies have shown that the GM displays endocrine organ functions, including the secretion of Serotonin (5-HT), dopamine, gamma-aminobutyric acid (GABA) and other neurotransmitters that control the HPA axis in athletes.¹⁰⁹ Alterations in the composition and function of the gut microbiota can therefore influence levels of these neurotransmitters, with potential implications for mood, cognition, and even muscle function. Several ways that the gut microbiome could influence neurotransmitter synthesis. One fascinating aspect is the direct production of neurotransmitters by certain gut bacteria. For example, specific strains within the *Lactobacillus* and *Bifidobacterium* genera have been shown to produce GABA.¹¹⁰ Similarly, some strains of *Escherichia coli*, typically associated with the gut, can synthesize dopamine.¹¹⁰ An indirect way the gut microbiome could alter neurotransmitter levels is through the production of precursor molecules, such as tryptophan, which is required for serotonin synthesis¹¹¹. This bidirectional communication not only performs the neurotransmitter synthesis, but in return, the neurotransmitter can also modulate gut microbial composition through the autonomic nervous system and neuroendocrine regulation.¹¹² For instance, reduced serotonin levels, often associated with an imbalanced gut microbiota, have been linked to fatigue and impaired exercise performance.¹¹³ GABA is also a key inhibitory neurotransmitter that can influence muscle tone and relaxation. For example, *Lactobacillus* and *Bifidobacterium* exhibit quite effective GABA production capacity.¹¹⁴ 5-HT is a neurohormone that is regulated by physical exercise.¹¹⁵ During intense exercise or competitive sports, high stress can affect GM composition through the release of neurotransmitters.¹¹⁶ It is also a major regulator of intestinal secretion and motility and is a key neurotransmitter in the gut-brain axis.¹¹⁷ The main strains that affect 5-HT synthesis are SCFAs, which are produced by bacteria belonging to Firmicutes and Bacteroidetes, the two most dominant phyla in human GM.¹¹⁸ Many studies have shown that 5-HT plays a multifaceted role in gut homeostasis, including immunity, inflammation regulation, and wound healing, and that probiotics function through the HPA axis to maintain health and alleviate exercise depletion and oxidation.¹⁵ Communication between the HPA and the gastrointestinal tract occurs through complex neuro-immune regulatory mechanisms. Neurotransmitters are received by the afferent vagus nerve and act on the hypothalamus and hippocampus regions of the brain, leading to the activation of the HPA.¹¹⁹ While the hypothalamic paraventricular nucleus (PVN) has neurons with neuroendocrine functions, the PVN interconnects with the bed nucleus of the stria terminalis (BNST) to synthesize corticotropin-releasing hormone (CRH). CRH is then released into the hypothalamic portal circulation and is transported to the anterior pituitary, which stimulates the release of adrenocorticotrophic hormone (ACTH) into the systemic circulation to regulate physical activity and participate in the control of stress responses.¹²⁰

Although the role of GM in the control of exercise-induced stress adaptation remains to be explored, GF animal experiments may provide a new insight into the role of GM in regulating the development and function of the HPA axis in response to stress. Anxiety-like behavior and neuroendocrine responses to acute stress were enhanced in GF rats compared to specific pathogen-free (SPF) controls.¹²¹ Hyperresponsiveness of the HPA axis was manifested by exaggerated release of corticosterone and ACTH induced by mild fasciculation stress, a process confirmed by enhanced expression of corticotropin-releasing factor in the hypothalamus and reduced expression of glucocorticoid receptor genes in the hippocampus.

The latest research provides new evidence that the hypothalamic neurons may directly sense the structural components of the GM to regulate feeding, nesting behavior and body temperature.¹⁰⁸ This study found out that the bacterial cell wall fragments derived from the intestinal microbiome can cross the intestinal barrier and enter the brain through blood circulation. Cell wall peptide acts on the pattern recognition receptor Nod2 (a pattern recognition receptor recognizing fragments of the bacterial cell wall termed muropeptides— develop alterations in food intake, nesting behavior, and body temperature control) in specific neurons in the hypothalamus, directly affecting the activity of these neurons.

In summary, through modulating vagus nerve afferent feedback, the GM can influence both brain and body function in this indirect way. And besides, it also has a direct way, which is a gut-brain communication mechanism to regulate the body's conditions. The GM is a critical modulator of muscle function, inflammation, and recovery processes through its production of bioactive metabolites, its impact on the immune system, and its bidirectional communication with the central nervous system via the gut-brain axis.

Probiotics

By definition, probiotics are living organisms that confer health benefits to their hosts by altering GM composition, improving gut barrier properties,¹²² antioxidant status,¹²³ and attenuating the inflammatory response¹²⁴ following exhaustive exercise. For example, in cross-sectional studies in humans, the gold standard measure of cardiorespiratory fitness, peak oxygen uptake (VO₂peak), showed a correlation with GM diversity and butyrate concentration, and enhanced abundance of the butyrate-producing bacteria *Clostridiales*, *Roseburia*, *Lachnospiraceae*, and *Erysipelotrichaceae* may contribute to butyrate increase in the concentration of butyrate.¹⁰⁹ This suggests that butyrate and butyrate-producing bacteria play an important role in aerobic exercisers. A study isolated a strain of *Veillonella atypica* that increased post-marathon abundance from the marathon runner's stool samples and transplantation to mice. The results showed that *V. atypica* enhanced athletic performance by converting exercise-induced metabolism of lactate into propionate.¹² In another inoculation study, strains *B. longum subsp. longum* OLP-01 and *Ligilactobacillus salivarius subsp. salicinius* SA-03, isolated from a female Olympic medalist in weightlifting, significantly increased forelimb grip strength and endurance capacity in a swim-to-exhaustion test in mice.^{125,126}

In endurance exercise review studies, the GM was shown to be key in controlling oxidative stress, and inflammatory responses as well as improving metabolism and energy expenditure during intense exercise.¹¹⁶ In addition, GM-producing N-butyrate modulates neutrophil function and migration to inhibit inflammatory cytokine-induced expression of vascular cell adhesion molecule-1, therefore strengthening the intestinal epithelial barrier and exerting an anti-inflammatory effect.¹²⁷ A sustainable competitive sport, such as triathlon, always results in muscle damage, leading to exercise-related oxidative stress, which will lead to a decrease in skeletal function. The two main aspects to induce exercise-induced muscle damage are mechanical and inflammatory stress.¹²⁸ *Lactobacillus plantarum* PS128 supplementation may be a potential ergogenic probiotic on triathletes for possible physiological adaptation and health promotion by significantly improving the expression of pro-inflammation cytokines (TNF- α , IFN- γ , IL-6, and IL-8), anti- (IL-10) inflammation cytokines, kidney injury (TRX and C5a), and oxidative stress (MPO) markers induced by intense exercise.¹²⁹

Prebiotic Like Effect Supplements

A prebiotic is an indigestible organic substance that can have beneficial effects on the host by selectively stimulating the growth or activity of one or a few species of bacteria in the colon, thereby enhancing host health. Including oligosaccharides,

polysaccharides, extracts of natural plants (such as vegetables, herbs, wild plants, etc.), and so on. Nowadays, such saponin, polysaccharides, and other components extracted from herbal medicines have been proven to exert a prebiotic effect such as *Lycium barbarum* polysaccharide (LBP), ginseng saponin, jiaogulan saponin,^{130–132} and so on.

Beyond exerted prebiotic effects, these organic substances also benefited exercise performance or exercise-related body conditions enhancement. In a recent study, *Platycodon grandiflorus* derived saponin enhances exercise function by ameliorating skeletal muscle protein synthesis and mitochondrial function. The potential mechanism is that saponin induced the expression of mitochondrial function proteins and increased the synthesis of skeletal muscle protein and muscle stem cell-related paired-box 7 and decreased the negative regulator myostatin, which indicates an enhancement of muscle regeneration.¹³³ Furthermore, *Platycodon grandiflorus* derived saponin attenuated the eccentric exercise-induced muscle damage through downregulating the muscle damage markers level including serum lactate dehydrogenase (LDH), creatinine kinase (CK) and C-related protein.¹³⁴ Ginseng is widely used and famous in the world, ginseng saponin also received the widely studied in the research laboratory. It is commonly suggested that it has the efficacy of improving performance on cognition and fatigue. *Panax ginseng* improved the speed of attention and some aspects of cognitive performance, although it lacks a further and clear mechanism of action and the paucity of sport-specific research.¹³⁵ But interestingly, the athletes ingested ginseng root extraction passed the urine test by the International Olympic Committee-approved laboratory, and there were no positive tests for any banned substances in any of the subjects.¹³⁶

Polysaccharide is another common ingredient in herbal medicines. LBP exerted a health protection effect for thousands of years in China. A recent study found that LBP is an important participant in the anti-oxidative process. After exhaustive exercise, the mean endurance time of treadmill running to exhaustion of rats in LBP treated groups was significantly prolonged and decreased the anti-oxidative index compared with that in the normal control group.¹³⁷ The role of polysaccharide in scavenging Reactive Oxygen Species (ROS) is likely associated with hydrogen and hydroxyl of the polysaccharide chain.¹³⁸

Taken together, these results provide a novel perspective on the biological function of homology of medicine and food against muscle damage and oxidation impairment. It is necessary to gain an insight into this project to help athletes make their body condition stronger and enhance performance. The schematic of probiotics that improves athletic performance through GM alteration is shown in Figure 4.

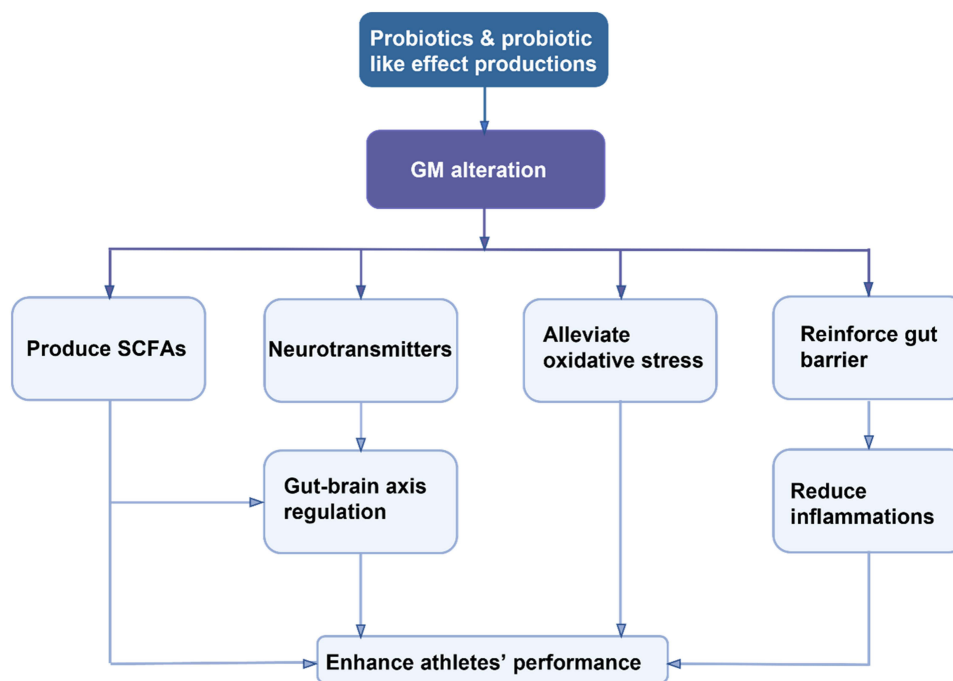


Figure 4 The schematic of how probiotics improves athletic performance through GM alteration.

Conclusion

Growing evidence from animal and human studies indicates that gut microbiota composition plays a crucial role in host physiology and athletic performance. This influence is multifaceted, with key mechanisms including the production of performance-enhancing metabolites like short-chain fatty acids, modulation of the gut-brain axis impacting mood and motivation, and regulation of immune responses crucial for recovery. Dietary patterns and exercise types further shape the gut microbial community, highlighting the interconnectedness of these factors. While moderate, consistent exercise generally promotes GM diversity and health, intense or prolonged exertion can disrupt this balance, potentially leading to dysbiosis and inflammation. There is a delicate balance between the nutritional intake, GM and athletes, and GM is the undisputed center of the three. Manipulating GM may be an optimal and safe dietary supplement strategy to improve athletes' health, training response, adaptations, and performance. Exploring the relationship between nutritional intake, GM and athletes is a fascinating project. It is impossible to separate physical activity and dietary supplementation; none of them can be omitted. Understanding this intricate relationship between GM, diet, and exercise is paramount for developing tailored nutritional strategies for athletes. By analyzing individual GM profiles, we can personalize diet and training regimens to optimize athletic performance, enhance recovery, and potentially mitigate the negative impacts of intense training. This personalized approach holds immense promise for athletes of all levels, from supporting sub-elite athletes in reaching their full potential to assisting elite athletes in pushing their limits, all while considering the unique needs of individuals with specific medical conditions.

In this work, we 1) make a comprehensive overview of the multifaceted relationship between the gut microbiome, exercise, and athletic performance. 2) Emphasized the crucial role of the gut-brain axis in mediating the interplay between the gut microbiome and athletic performance. This bidirectional communication pathway is often overlooked in studies focusing solely on metabolic aspects. 3) Highlighted exercise intensity, which is an important consideration, as most research focuses on either moderate exercise or intense training, without directly comparing their impacts. 4) And our synthesis acknowledges both the beneficial effects of moderate exercise and the potential downsides of intense training on gut health. This balanced perspective is crucial for developing well-rounded recommendations for athletes.

By addressing these points, our work can make a valuable contribution to the field by providing a nuanced understanding of the gut microbiome's role in athletic performance and guiding future research towards personalized interventions for athletes.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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